

Gastroretentive drug delivery systems: a review

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The purpose of writing this review on gastroretentive drug delivery systems was to compile the recent literature with special focus on various gastroretentive approaches that have recently become leading methodologies in the field of site-specific orally administered controlled release drug delivery. In order to understand various physiological difficulties to achieve gastric retention, we have summarized important factors controlling gastric retention. Afterwards, we have reviewed various gastroretentive approaches designed and developed until now, i.e. high density (sinking), floating, bio- or mucoadhesive, expandable, unfoldable, super porous hydrogel and magnetic systems. Finally, advantages of gastroretentive drug delivery systems were covered in detail.

Keywords: Gastric retention, Oral controlled release, Floating dosage form, Drug delivery system.

INTRODUCTION

Oral administration is the most convenient and preferred means of any drug delivery to the systematic circulation. Oral controlled release drug delivery have recently been of increasing interest in pharmaceutical field to achieve improved therapeutic advantages, such as ease of dosing administration, patient compliance and flexibility in formulation. Drugs that are easily absorbed from gastrointestinal tract (GIT) and have short half-lives are eliminated quickly from the systemic circulation. Frequent dosing of these drugs is required to achieve suitable therapeutic activity. To avoid this limitation, the development of oral sustained-controlled release formulations is an attempt to release the drug slowly into the gastrointestinal tract (GIT) and maintain an effective drug concentration in the systemic circulation for a long time. After oral administration, such a drug delivery would be retained in the stomach and release the drug in a controlled manner, so that the drug could be supplied continuously to its absorption sites in the gastrointestinal tract (GIT) [1]. These drug delivery systems suffer from mainly two adversities: the short gastric retention time (GRT) and unpredictable short gastric emptying time (GET), which can result in incomplete drug release from the dosage form in the absorption zone (stomach or upper part of small intestine) leading to diminished efficacy of administered dose [2]. To formulate a site-specific orally administered controlled release dosage form, it

is desirable to achieve a prolong gastric residence time by the drug delivery. Prolonged gastric retention improves bioavailability, increases the duration of drug release, reduces drug waste, and improves the drug solubility that are less soluble in a high pH environment [3]. Also prolonged gastric retention time (GRT) in the stomach could be advantageous for local action in the upper part of the small intestine e.g. treatment of peptic ulcer, etc.

Gastroretentive drug delivery is an approach to prolong gastric residence time, thereby targeting site-specific drug release in the upper gastrointestinal tract (GIT) for local or systemic effects. Gastroretentive dosage forms can remain in the gastric region for long periods and hence significantly prolong the gastric retention time (GRT) of drugs. Over the last few decades, several gastroretentive drug delivery approaches being designed and developed, including: high density (sinking) systems that is retained in the bottom of the stomach [4], low density (floating) systems that causes buoyancy in gastric fluid [5, 6, 7], mucoadhesive systems that causes bioadhesion to stomach mucosa [8], unfoldable, extendible, or swellable systems which limits emptying of the dosage forms through the pyloric sphincter of stomach [9, 10], superporous hydrogel systems [11], magnetic systems [12] etc. The current review deals with various gastroretentive approaches that have recently become leading

methodologies in the field of site-specific orally administered controlled release drug delivery systems.

FACTORS CONTROLLING GASTRIC RETENTION OF DOSAGE FORMS

The stomach anatomy and physiology contain parameters to be considered in the development of gastroretentive dosage forms. To pass through the pyloric valve in to the small intestine the particle size should be in the range of 1 to 2 mm ^[13]. The most important parameters controlling the gastric retention time (GRT) of oral dosage forms include : density, size and shape of the dosage form, food intake and its nature, caloric content and frequency of intake, posture, gender, age, sex, sleep, body mass index, physical activity and diseased states of the individual (e.g. chronic disease, diabetes etc.) and administration of drugs with impact on gastrointestinal transit time for example drugs acting as anticholinergic agents (e.g. atropine, propantheline), Opiates (e.g. codeine) and prokinetic agents (e.g. metoclopramide, cisapride.) ^[14]. The molecular weight and lipophilicity of the drug depending on its ionization state are also important parameters ^[15].

Density of dosage forms

The density of a dosage form also affects the gastric emptying rate and determines the location of the system in the stomach. Dosage forms having a density lower than the gastric contents can float to the surface, while high density systems sink to bottom of the stomach ^[16]. Both positions may isolate the dosage system from the pylorus. A density of $< 1.0 \text{ gm/ cm}^3$ is required to exhibit floating property ^[17].

Shape and size of the dosage form

Shape and size of the dosage forms are important in designing indigestible single unit solid dosage forms. The mean gastric residence times of non-floating dosage forms are highly variable and greatly dependent on their size, which may be large, medium and small units. In most cases, the larger the dosage form the greater will be the gastric

retention time (GRT) due to the larger size of the dosage form would not allow this to quickly pass through the pyloric antrum into the intestine ^[18]. Dosage forms having a diameter of more than 7.5 mm show a better gastric residence time compared with one having 9.9 mm ^[17]. Ring-shaped and tetrahedron-shaped devices have a better gastric residence time as compared with other shapes ^[19].

Food intake and its nature

Food intake, viscosity and volume of food, caloric value and frequency of feeding have a profound effect on the gastric retention of dosage forms. The presence or absence of food in the gastrointestinal tract (GIT) influences the gastric retention time (GRT) of the dosage form. Usually the presence of food in the gastrointestinal tract (GIT) improves the gastric retention time (GRT) of the dosage form and thus, the drugs absorption increases by allowing its stay at the absorption site for a longer period. Again, increase in acidity and caloric value shows down gastric emptying time (GET), which can improve the gastric retention of dosage forms ^[20].

Effect of gender, posture and age

Generally females have slower gastric emptying rates than male. The effect of posture does not have any significant difference in the mean gastric retention time (GRT) for individuals in upright, ambulatory and supine state. In case of elderly persons, gastric emptying is slowed down ^[21].

POTENTIAL DRUG CANDIDATES FOR GASTRORETENTIVE DRUG DELIVERY SYSTEMS

- 1) Drugs those are locally active in the stomach e.g. misoprostol, antacids etc.
- 2) Drugs that have narrow absorption window in gastrointestinal tract (GIT) e.g. L-DOPA, para aminobenzoic acid, furosemide, riboflavin etc.
- 3) Drugs those are unstable in the intestinal or colonic environment e.g. captopril, ranitidine HCl, metronidazole.
- 4) Drugs that disturb normal colonic microbes e.g.

antibiotics against *Helicobacter pylori*.

- 5) Drugs that exhibit low solubility at high pH values e.g. diazepam, chlorthalidone, verapamil HCl.

DRUGS THOSE ARE UNSUITABLE FOR GASTRORETENTIVE DRUG DELIVERY SYSTEMS

- 1) Drugs that have very limited acid solubility e.g. phenytoin etc.
- 2) Drugs that suffer instability in the gastric environment e.g. erythromycin etc.
- 3) Drugs intended for selective release in the colon e.g. 5- amino salicylic acid and corticosteroids etc.

APPROACHES TO ACHIEVE GASTRIC RETENTION

High density (sinking) system or non- floating drug delivery system

This approach involves formulation of dosage forms with the density that must exceed density of normal stomach content ($\sim 1.004 \text{ gm/cm}^3$). These formulations are prepared by coating drug on a heavy core or mixed with inert materials such as iron powder, barium sulphate, zinc oxide and titanium oxide etc [22]. The materials increase density by up to 1.5- 2.4 gm/cm^3 . A density close to 2.5 gm/cm^3 seems necessary for significant prolongation of gastric residence time [23]. But, effectiveness of this system in human beings was not observed [24] and no system has been marketed.

Floating drug delivery systems

Floating drug delivery systems is one of the important approaches to achieve gastric retention to obtain sufficient drug bioavailability [25]. This delivery systems is desirable for drugs with an absorption window in the stomach or in the upper small intestine [26]. This have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting gastric emptying rate for a prolonged period and the drug is released slowly

as a desired rate from the system. After release of drug, the residual system is emptied from the stomach. This result in an increased gastric retention time (GRT) and a better control of the fluctuation in plasma drug concentration. The major requirements for floating drug delivery system are [22].

- It should release contents slowly to serve as a reservoir.
- It must maintain specific gravity lower than gastric contents (1.004 – 1.01 gm/cm^3).
- It must form a cohesive gel barrier.

The inherent low density can be provided by the entrapment of air (e.g. hollow chambers) [27] or by the incorporation of low density materials (e.g. fatty materials or oils, or foam powder) [5, 28, 29]. These following approaches have been used for the design of floating dosage forms of single and multiple-unit systems. Recently a single-unit floating system was proposed consisting of polypropylene foam powder, matrix forming polymers, drug and filler [30]. The good floating behavior of these systems could be successfully combined with accurate control of the resulting drug release patterns. Single-unit dosage forms are associated with problems such as sticking together or being obstructed in the gastrointestinal tract (GIT) which may produce irritation. On the other hand multiple-unit floating systems may be an attractive alternative since they have been shown to reduce the inter- and intra- subject availabilities in drug absorption as well as to lower the possibility of dose dumping [26]. Various multiple-unit floating system like air compartment multiple-unit system [2], hollow microspheres (microballoons) prepared by the emulsion solvent diffusion method [31], microparticles based on low density foam powder [5], beads prepared by emulsion gelatin method [32] etc. can be distributed widely throughout the GIT, providing the possibility of achieving a longer lasting and more reliable release of drugs. Based on the mechanism of buoyancy two distinctly different technologies, i.e. non-effervescent and effervescent systems have been utilized in the development of floating drug delivery system.

Non-effervescent Systems

Non-effervescent floating drug delivery systems are normally prepared from gel-forming or highly swellable cellulose type hydrocolloids, polysaccharides or matrix forming polymers like polyacrylate, polycarbonate, polystyrene and polymethacrylate. In one approach, intimate mixing of drug with a gel forming hydrocolloid which results in contact with gastric fluid after oral administration and maintain a relative integrity of shape and a bulk density less than unity within the gastric environment [33]. The air trapped by the swollen polymer confers buoyancy to these dosage forms. Excipients used most commonly in these systems include hydroxypropyl methylcellulose (HPMC) polyacrylates, polyvinyl acetate, carbopol, agar, sodium alginate, calcium chloride, polyethylene oxide and polycarbonates [3]. This system can be further divided into the sub-types:

Hydrodynamically balanced systems: Sheth and Tossounian [34] first designated these 'hydrodynamically balanced systems'. These systems contains drug with gel-forming hydrocolloids meant to remain buoyant on the stomach content. These are single-unit dosage form, containing one or more gel-forming hydrophilic polymers. Hydroxypropyl methylcellulose (HPMC), hydroxethyl cellulose (HEC), hydroxypropyl cellulose (HPC), sodium carboxymethyl cellulose (NaCMC), polycarbophil, polyacrylate, polystyrene, agar, carrageenans or alginic acid are commonly used excipients to develop these systems [35, 36]. The polymer is mixed with drugs and usually administered in hydrodynamically balanced system capsule. The capsule shell dissolves in contact with water and mixture swells to form a gelatinous barrier, which imparts buoyancy to dosage form in gastric juice for a long period. Because, continuous erosion of the surface allows water penetration to the inner layers maintaining surface hydration and buoyancy to dosage form [36]. Incorporation of fatty excipients gives low-density formulations reducing the erosion. Madopar LP[®], based on the system was marketed during the 1980's [37]. Effective drug deliveries depend on the balance of drug loading and the effect of polymer on its release profile.

Several strategies have been tried and investigated to improve efficiencies of the floating hydrodynamically balanced systems [36, 37].

Microballoons / Hollow microspheres: Microballoons / hollow microspheres loaded with drugs in their other polymer shell were prepared by simple solvent evaporation or solvent diffusion / evaporation methods [38] (Figure 1) to prolong the gastric retention time (GRT) of the dosage form. Commonly used polymers to develop these systems are polycarbonate, cellulose acetate, calcium alginate, Eudragit S, agar and low methoxylated pectin etc. Buoyancy and drug release from dosage form are dependent on quantity of polymers, the plasticizer polymer ratio and the solvent used for formulation. The microballoons floated continuously over the surface of an acidic dissolution media containing surfactant for >12 hours [3]. At present hollow microspheres are considered to be one of the most promising buoyant systems because they combine the advantages of multiple-unit system and good floating.

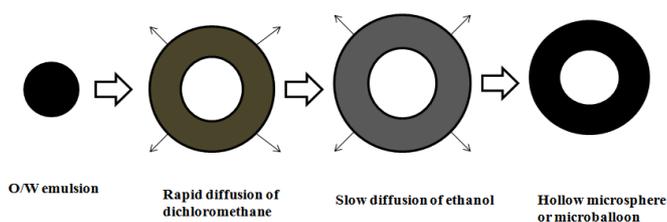


Figure 1. Formulation of floating hollow microsphere or microballoon

Alginate beads: Talukdar and Fassihi [32] recently developed a multiple-unit floating system based on cross-linked beads. They were made by using Ca^{2+} and low methoxylated pectin (anionic polysaccharide) or Ca^{2+} low methoxylated pectin and sodium alginate. In this approach, generally sodium alginate solution is dropped into aqueous solution of calcium chloride and causes the precipitation of calcium alginate. These beads are then separated and dried by air convection and freeze drying, leading to the formulation of a porous system, which can maintain a floating force for over 12 hrs. These beads improve gastric retention time (GRT) more than 5.5 hrs [3, 39].

Microporous compartment system: This approach

is based on the principle of the encapsulation of a drug reservoir inside a microporous compartment with pores along its top and bottom walls [40]. The peripheral walls of the device were completely sealed to prevent any direct contact of the gastric surface with the undissolved drug. In the stomach the floatation chamber containing entrapped air causes the delivery system to float in the gastric fluid [22]. Gastric fluid enters through the aperture, dissolves the drug and causes the dissolved drug for continuous transport across the intestine for drug absorption.

Effervescent (gas generating) systems

Floatability can be achieved by generation of gas bubbles. These buoyant systems utilize matrices prepared with swellable polymers such as polysaccharides (e.g. chitosan), effervescent components (e.g. sodium bicarbonate, citric acid or tartaric acid) [40]. The optimal stoichiometric ratio of citric acid and sodium bicarbonate for gas generation is reported to be 0.76: 1 [19]. In this system carbon dioxide is released and causes the formulation to float in the stomach (Figure 2 and Figure 3). Other approaches and materials that have been reported are a mixture of sodium alginate and sodium bicarbonate, multiple unit floating dosage forms that generate gas (carbon dioxide) when ingested, floating mini capsules with a core of sodium bicarbonate, lactose and polyvinyl pyrrolidone (PVP) coated with hydroxypropyl methylcellulose (HPMC), and floating system based on ion exchange resin technology etc [3]. Bilayer or multilayer system has also been designed [41, 42]. Drugs and excipients can be formulated independently and the gas generating material can be incorporated in to any of the layers. Further modifications involve coating of the matrix with a polymer which is permeable to water, but not to carbon dioxide. The main difficulty of these formulations is finding a good compromise between elasticity, plasticity and permeability of the polymers.

Bioadhesive or Mucoadhesive drug delivery systems

Bioadhesive drug delivery systems are used as a

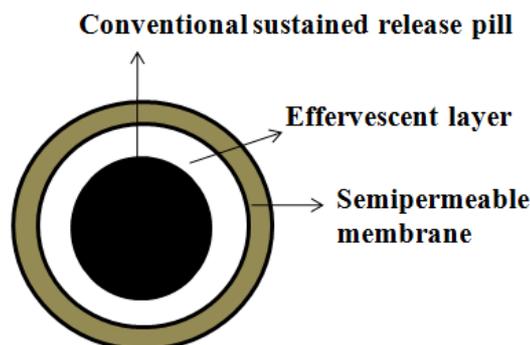


Figure 2. Effervescent (gas generating) systems

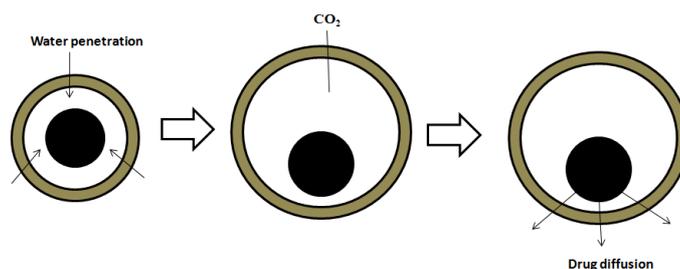


Figure 3. Drug release from effervescent (gas generating) systems

delivery device within the human to enhance drug absorption in a site-specific manner. In this approach, bio adhesive polymers are used and they can adhere to the epithelial surface in the stomach [43]. Thus, they improve the prolongation of gastric retention. The basis of adhesion in that a dosage form can stick to the mucosal surface by different mechanism. These mechanisms [44, 45] are:

- 1) The wetting theory, which is based on the ability of bioadhesive polymers to spread and develop intimate contact with the mucous layers.
- 2) The diffusion theory, which proposes physical entanglement of mucin strands the flexible polymer chains, or an interpenetration of mucin strands into the porous structure of the polymer substrate.
- 3) The absorption theory, suggests that bioadhesion is due to secondary forces such as Vander Waal forces and hydrogen bonding.
- 4) The electron theory, which proposes attractive electrostatic forces between the glycoprotein mucin net work and the bio adhesive material.

Materials commonly used for bioadhesion are poly acrylic acid, chitosan, cholestyramine, sodium alginate, hydroxypropyl methylcellulose (HPMC), sucralfate, tragacanth, dextrin, polyethylene glycol

(PEG) and polylactic acids etc. Even though some of these polymers are effective at producing bioadhesive, it is very difficult to maintain it effectively because of the rapid turnover of mucus in the gastrointestinal tract (GIT).

Expandable, unfoldable and swellable systems

A dosage form in the stomach will withstand gastric transit if it bigger than pyloric sphincter. However, the dosage form must be small enough to be swallowed, and must not cause gastric obstruction either singly or by accumulation. Thus, their configurations [46, 47] are required to develop an expandable system to prolong gastric retention time (GRT):

- 1) a small configuration for oral intake,
- 2) an expanded gastroretentive form, and
- 3) a final small form enabling evacuation following drug release from the device.

Thus, gastroretentivity is improved by the combination of substantial dimension with high rigidity of dosage form to withstand peristalsis and mechanical contractility of the stomach. Unfoldable and swellable systems have been investigated and recently tried to develop an effective gastroretentive drug delivery. Unfoldable systems are made of biodegradable polymers. They are available in different geometric forms like tetrahedron, ring or planner membrane (4 - label disc or 4 - limbed cross form) of bioerodible polymer compressed within a capsule which extends in the stomach [48, 49]. Swellable systems are also retained in the gastro intestinal tract (GIT) due to their mechanical properties. The swelling is usually results from osmotic absorption of water and the dosage form is small enough to be swallowed by the gastric fluid (Figure 4). Expandable systems have some drawbacks like problematical storage of much easily hydrolysable, biodegradable polymers relatively short-lived mechanical shape memory for the unfolding system most difficult to industrialize and not cost effective.⁵⁰ Again, permanent retention of rigid, large single-unit expandable drug delivery dosage forms may cause brief obstruction, intestinal

adhesion and gastropathy [19].

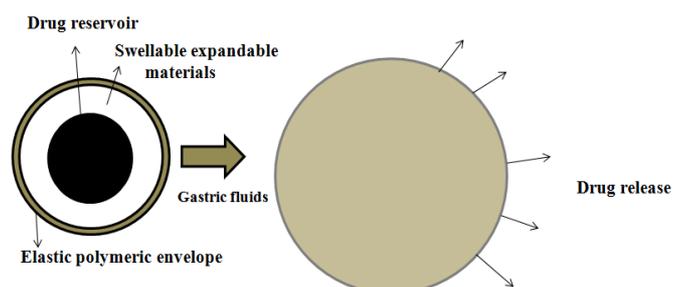


Figure 4. Drug release from swellable systems

Super porous hydrogel systems

These swellable systems differ sufficiently from the conventional types to warrant separate classification. In this approach to improve gastric retention time (GRT) super porous hydrogels of average pore size >100 micro meter, swell to equilibrium size within a minute due to rapid water uptake by capillary wetting through numerous interconnected open pores [51]. They swell to a large size (swelling ratio: 100 or more) and are intended to have sufficient mechanical strength to withstand pressure by gastric contraction. This is advised by co-formulation of hydrophilic particulate material [52].

Magnetic Systems

This approach to enhance the gastric retention time (GRT) is based on the simple principle that the dosage form contains a small internal magnet, and a magnet placed on the abdomen over the position of the stomach. Although magnetic system seems to work, the external magnet must be positioned with a degree of precision that might compromise patient compliance [45].

Commonly used drugs in formulation of gastroretentive dosage forms and some gastroretentive products available in the market are listed in Table 1 and Table 2 respectively.

ADVANTAGES OF GASTRORETENTIVE DRUG DELIVERY SYSTEMS

Table 1. Commonly used drug in formulation of gastro retentive dosages forms [17, 22]

| Dosage forms | Drugs |
|------------------------------|---|
| Floating Tablets | Acetaminophen, Acetylsalicylic acid, Ampicillin, Amoxicillin trihydrate, Atenolol, Captopril, Cinnerzine, Chlorpheniramine maleate, Ciprofloxacin, Diltiazem, Fluorouracil, Isosorbide dinitrate, Isosorbide mononitrate, p-Aminobenzoic acid(PABA), Prednisolone, Nimodipine, Sotalol, Theophylline, Verapamil |
| Floating Capsules | Chlordiazepoxide HCl, Diazepam, Furosemide, L-DOPA and Benserazide, Nicardipine, Misoprostol, Propranolol, Pepstatin |
| Floating Microspheres | Aspirin, Griseofulvin, p-nitro aniline, Ibuprofen, Terfenadine, Tranilast |
| Floating Granules | Diclofenac sodium, Indomethacin, Prednisolone |
| Powders | Several basic drugs |
| Films | Cinnerzine |

Table 2. Gastroretentive products available in the market [22, 53]

| Brand Name | Active Ingredient(s) |
|--------------------------------|-----------------------------|
| Cifran OD [®] | Ciprofloxacin |
| Madopar [®] | L-DOPA and Benserazide |
| Valrelease [®] | Diazepam |
| Topalkan [®] | Aluminum -magnesium antacid |
| Almagate FlatCoat [®] | Aluminum -magnesium antacid |
| Liquid Gavison [®] | Aluminium hydroxide, |
| Conviron | Ferrous sulfate |
| Cytotec [®] | Misoprostal |

- 1) The bioavailability of therapeutic agents can be significantly enhanced especially for those which get metabolized in the upper GIT by this gastroretentive drug delivery approach in comparison to the administration of non-gastroretentive drug delivery. There are several different factors related to absorption and transit of the drug in the gastrointestinal tract (GIT) that act concomitantly to influence the magnitude of drug absorption [54].
- 2) For drugs with relatively short half life, sustained release may result in a flip-flop pharmacokinetics and also enable reduced frequency of dosing with improved patient compliance.
- 3) They also have an advantage over their conventional system as it can be used to overcome the adversities of the gastric retention time (GRT) as well as the gastric emptying time (GET). As these systems are expected to remain

buoyant on the gastric fluid without affecting the intrinsic rate of employing because their bulk density is lower than that of the gastric fluids.

- 4) Gastroretentive drug delivery can produce prolong and sustain release of drugs from dosage forms which avail local therapy in the stomach and small intestine. Hence they are useful in the treatment of disorders related to stomach and small intestine.
- 5) The controlled, slow delivery of drug form gastroretentive dosage form provides sufficient local action at the diseased site, thus minimizing or eliminating systemic exposure of drugs. This site-specific drug delivery reduces undesirable effects of side effects.
- 6) Gastroretentive dosage forms minimize the fluctuation of drug concentrations and effects. Therefore, concentration dependent adverse effects that are associated with peak concentrations can be presented. This feature is of special importance for drug with a narrow therapeutic index [55].
- 7) Gastroretentive drug delivery can minimize the counter activity of the body leading to higher drug efficiency.
- 8) Reduction of fluctuation in drug concentration makes it possible to obtain improved selectivity in receptor activation.
- 9) The sustained mode of drug release from Gastroretentive doses form enables extension of the time over a critical concentration and thus enhances the pharmacological effects and improves the chemical outcomes.

CONCLUSION

Based on the literature surveyed, it may be concluded that gastroretentive drug delivery offers various potential advantages for drug with poor bioavailability due their absorption is restricted to the upper gastrointestinal tract (GIT) and they can be delivered efficiently thereby maximizing their absorption and enhancing absolute bioavailability. Due to complexity of pharmacokinetics and pharmacodynamics parameters, *in vivo* studies are required to establish the optional dosage form for a specific drug. Another promising area of research for gastroretentive drug delivery system is eradication of *Helicobacter pylori*, which is now believed to be causative bacterium of chronic

gastritis and peptic ulcers. Although, this micro organism is highly sensitive to many antibiotics, its complete eradication requires high concentration of antibiotics be maintained within gastric mucosa for prolonged time period. An important feature to take into account is the stomach physiology. The time when the drug is taken (during or apart from the meal) is an important parameter. To develop an efficient gastroretentive dosage form is a real challenge to pharmaceutical technology. Indeed, the drug delivery system must remain for a sufficient time in the stomach, which is not compatible with its normal physiology. All these gastroretentive drug delivery systems (high density, floating, expandable or unfoldable or swelling, superporous, bioadhesive, magnetic systems etc.) are interesting and present their own advantages and disadvantages. Now, a lot of work is running to develop different types of gastroretentive delivery systems of various drugs. In the future, it is expected that they will become of increasing importance, ultimately leading to improved efficiencies of various types of pharmacotherapies.

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